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EXAMINER	
DUFFY, BRADLEY	
ART UNIT	**PAPER NUMBER**
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/508,978	HWU ET AL.	
	Examiner	Art Unit	
	Brad Duffy	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8,11-22,25,28-30,58-63,66 and 67* is/are pending in the application.

4a) Of the above claim(s) *1-5,8,11-22,25,28-30,58 and 60-63* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *59,66 and 67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/8/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed August 8, 2007, is acknowledged and has been entered. Claims 31-38 and 57 have been canceled. Claim 59 has been amended. Claims 66 and 67 have been newly added.

2. Claims 1-5, 8, 11-22, 25, 28-30, 58-63, 66, and 67 are pending in the application and currently under prosecution.

3. Claims 1-5, 8, 11-22, 25, 28-30, 58 and 60-63 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on January 18, 2007.

4. Claims 59, 66 and 67 are under examination.

5. The following Office action contains NEW GROUNDS of rejection and objection necessitated by amendment.

Information Disclosure Statement

6. The references cited in the information disclosure statement filed on August 8, 2007, have been considered.

Priority

7. With respect to the issue of priority, Applicant has not submitted any evidence or arguments in the reply filed August 8, 2007 that claims 59, 66 and 67 should receive benefit under USC §§ 119 and/or 120 of the earlier filing date of the 60/368,438, filed March 27, 2002.

As previously explained, the claims do not properly benefit under 35 U.S.C. § 120 by the earlier filing dates of the priority document claimed, since those claims are

rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and/or a sufficiently enabling disclosure.

Again, to receive benefit of the earlier filing date under 35 USC §§ 119 and/or 120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Accordingly, the effective filing date of the claims is deemed the filing date of PCT/US03/09707, namely March 23, 2003.

Grounds of Objection and Rejection Withdrawn

8. Unless specifically reiterated below, Applicant's amendment and/or arguments filed August 8, 2007, have obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed April 12, 2007.

Response to the Declaration under 37 C.F.R. § 1.132

9. The declaration under 37 C.F.R. § 1.132 filed April 24, 2007 is insufficient to overcome the rejection of claims 59, 66 and 67 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for the following reasons:

The declaration states co-inventor Warren Leonard's largely unsubstantiated opinion that mouse model data is generally predictive of the biological activity of a molecule in a human context, and that based on the data presented in the specification, a polynucleotide encoding human IL-21 would likely induce apoptosis in human cells. The declaration provides no factual evidence supporting the stated opinion, or which fairly rebuts the Office's position that the specification is not reasonably enabling of the use of the claimed invention, per the requirements set forth under § 112, first paragraph.

Furthermore, the claims are drawn to methods of inducing apoptosis of a natural killer (NK) cell comprising contacting the NK cells with a polynucleotide encoding (i)

SEQ ID NO: 6 or 8, (ii) a variant of SEQ ID NO: 6 or 8, wherein the variant has an amino acid sequence that is greater than 95% identical to the amino acid sequence of SEQ ID NO: 6 or 8, or (iii) a fragment of about 5 to about 30 amino acids of SEQ ID NO: 6 or 8, wherein the fragment retains the biological activity of SEQ ID NO: 6 or 8, in an amount effective to induce apoptosis of the NK cell. Thus, the opinion expressed by Dr. Leonard in the declaration even fails to address the full breadth of the claims.

As such, there is presently a preponderance of evidence now of record, which suggests contrary to the stated opinion of Dr. Leonard that the claimed invention could not be used to achieve the claimed effect without undue and/or unreasonable experimentation.

For example, the previous Office action cites Parrish-Novak et al (J. Leukoc. Biol., 72:856-863, 2002, of record) as providing evidence showing that human natural killer cells have fundamental differences, when compared to murine natural killer cells, in response to human or mouse IL-21, respectively. Therefore, it is submitted that the levels of skill and unpredictability in the art are such that even if the claims were substantially more limited, it is not apparent that the human IL-21 polynucleotide would have a similar effect on human NK cells, and so the claimed invention could not be used to achieve the claimed effect without undue and/or unreasonable experimentation.

Thus, although the merit of the declaration under 37 C.F.R. § 1.132 has been carefully considered, it is for these reasons that it is deemed insufficient to overcome the rejection of claims 59, 66 and 67 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

Grounds of Objection Maintained

10. The objection to the specification because the use of improperly demarcated trademarks is maintained. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Although it appears that Applicant has made a *bona fide* attempt to resolve this issue by appropriately amending the specification, additional examples of improperly demarcated trademarks appearing in the specification are noted, namely GenBank® (see e.g., page 1, paragraph [0003] and page 5, paragraph [0021]).

Again, appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at <http://www.uspto.gov/web/menu/search.html>.

Grounds of Rejection Maintained

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. The rejection of claims 59, 66 and 67 under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for using** a method for inducing apoptosis of murine natural killer cells *in vivo*, said method comprising contacting said natural killer cells with a plasmid comprising a polynucleotide encoding SEQ ID NO:8[1], wherein said polynucleotide induces apoptosis of said natural killer cells, **does not reasonably provide enablement for using** a method for inducing apoptosis of natural killer cells in humans or other animal species **and does not reasonably provide enablement for using** any other methods encompassed by the claims, which are broadly but reasonably interpreted to include, for example, "gene therapy" (i.e., the *in*

[1] The amino acid sequence of SEQ ID NO:8 provides the murine interleukin 21 amino acid sequence (see page 12 of the response filed August 8, 2007) and therefore, a polynucleotide encoding SEQ ID NO:8 is analogous to a polynucleotide that was cloned with murine IL-21 primers consisting of SEQ ID NO:3 and

vivo delivery of genetic information to targeted cells within a body using naked DNA or viral vectors or by reintroducing *ex vivo* modified host cells into the body, so as to achieve clinical or therapeutic effect), is maintained. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

Beginning at page 14 of the amendment filed August 8, 2007, Applicant has traversed the propriety of maintaining this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Contrary to Applicant's arguments, the specification, as filed, would not reasonably enable the skilled artisan to use the claimed methods of inducing apoptosis of a natural killer (NK) cell comprising contacting the NK cell with a polynucleotide encoding (i) SEQ ID NO: 6 or 8, (ii) a variant of SEQ ID NO: 6 or 8, wherein the variant has an amino acid sequence that is greater than 95% identical to the amino acid sequence of SEQ ID NO: 6 or 8, or (iii) a fragment of about 5 to about 30 amino acids of SEQ ID NO: 6 or 8, wherein the fragment retains the biological activity of SEQ ID NO: 6 or 8, in an amount effective to induce apoptosis of the NK cell without undue and/or unreasonable experimentation.

In this case, the Applicant has argued that the specification provides ample amounts of direction and guidance for practicing the inventive method *in vitro* or *in vivo* at e.g., paragraphs [0091] to [0096] and paragraphs [0100] to [0105], and that the Examiner has not met the burden to establish that the claims are not enabled.

In response, while paragraphs [0091] to [0096] provide methods for cloning the human and murine IL-21 polynucleotides using nucleotide primers, and paragraphs [0100] to [0105] teach methods of administering plasmid DNA encoding the murine IL-21 polynucleotide to mice increases apoptosis of NK cells in those mice, the disclosure does not reasonably enable the full scope of the claims which encompasses contacting

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SEQ ID NO:4 which encodes a murine IL-21 polypeptide, which was referred to in the previous Office

any NK cell from any species with a polynucleotide encoding (i) SEQ ID NO: 6 or 8, (ii) a variant of SEQ ID NO: 6 or 8, wherein the variant has an amino acid sequence that is greater than 95% identical to the amino acid sequence of SEQ ID NO: 6 or 8, or (iii) a fragment of about 5 to about 30 amino acids of SEQ ID NO: 6 or 8, wherein the fragment retains the biological activity of SEQ ID NO: 6 or 8, in an amount effective to induce apoptosis of the NK cell. For example, while the Il-21 polynucleotide variants have been limited to those that encode polypeptides with greater than 95% identity to SEQ ID NO: 6 or 8 and the IL-21 polynucleotide fragments have been limited to IL-21 polynucleotide fragments that encode fragments of about 5 to about 30 amino acids of SEQ ID NO: 6 or 8 the specification does not provide any specific non-general guidance that would allow one of skill in the art make polynucleotides commensurate in scope of the claims as the specification does not provide any specific guidance identifying regions of the murine Il-21 polynucleotide that are effective to induce apoptosis in NK cells from any species and therefore, one of skill in the art would be subject to undue experimentation to practice the claimed invention. Notably, as set forth in the previous Office action at page 16, one of skill in the art could not extrapolate the results obtained by injecting mice with a plasmid comprising the murine polynucleotide that encodes SEQ ID NO:8, which increases apoptosis of murine NK cells, to the use of polynucleotides encoding SEQ ID NO:6 or SEQ ID NO:8, their fragments or variants to practice the claimed invention on any NK cell *in vitro* or *in vivo* in any species without undue experimentation.

Additionally, to further address Applicant's argument that the Examiner has not established that the specification does not enable the use of the claimed polynucleotides for *in vivo* gene therapy methods to induce apoptosis of NK cells in humans because the Examiner's argument is not specific for the claimed invention, the Examiner notes that, as set forth in the previous Office action at page 14, the specification sets forth gene therapy methods of administering IL-21 polynucleotides to humans (see paragraphs [0043], [0045] and [0051]. Furthermore, in the response filed

August 8, 2007 at page 15, 1st paragraph, the claimed method is defined as one that could take place *in vitro* or *in vivo* and this response sets forth that the NK cells of the claimed method are not limited to any particular type of NK cells. Finally, as evidenced by Wang et al (Cancer Research, 63:9016-9022, 2003, of record) in the previous office action at page 15, such gene therapy techniques of administering a IL-21 polynucleotides for the treatment of humans do not appear practical. Thus, the Examiner disagrees with Applicant's assertion that the rejection is not specific to the claimed invention because the breadth encompassed by the claims in light of by the disclosure is not enabled and the references cited by the Examiner are specific to this rejection. Therefore, the Examiner maintains that one of skill in the art would be subject to undue experimentation to practice *in vivo* gene therapy methods to induce apoptosis of NK cells in humans as encompassed by the claims. Notably, the specification lacks any specific non-general guidance on how to induce apoptosis of NK cells in humans using the claimed methods.

Finally, as set forth above, Dr. Leonard's declaration under 37 CFR 1.312 sets forth opinion that mouse models are predictive of the biological activity of a molecule in a human context, and that as such he *believes* that a polynucleotide encoding human IL-21 would *likely* induce apoptosis in human cells, based on the mouse model data provided in the instant application.

Although the merit of the declaration by Dr. Leonard has been carefully considered, the stated opinion is unsubstantiated by a showing of factual evidence or sound scientific reasoning; moreover, it fails even to address the full breadth of the claims, which are directed to a method for selectively inducing the apoptosis of natural killer cells of any of a plurality of animal species, including humans, either *in vitro* or *in vivo*, because it simply states that it is Dr. Leonard's belief that "a polynucleotide encoding human IL-21 would likely induce apoptosis in human cells" (item # 3 of the declaration).

Notably, as evidenced by Parrish-Novak et al (J. Leukoc. Biol., 72:856-863, 2002, of record), and explained in the previous Office action, human natural killer cells have fundamental differences, when compared to murine natural killer cells, in response

to the human or mouse IL-21 polypeptide, respectively. While, the response filed August 8, 2007, at page 16 argues that one could reasonably predict what would occur in a human based on mouse model data because Parrish-Novak et al speculate that the IL-21 polypeptide may have a similar activities on murine and human NK cells when dose, stage and activation state are matched, it is noted Parrish-Novak et al teach that laboratory mice have relatively naïve natural killer cells when compared to human natural killer cells because human natural killer cells are exposed to significantly more environmental antigens. Thus, as the specification does not reasonably establish that the murine natural killer cells that undergo apoptosis in response to a plasmid comprising a polynucleotide encoding SEQ ID NO:8 are reasonably matched to human NK cells, it is not apparent that the results obtained in mice would be predictive of the response of human natural killer cells to a polynucleotide encoding SEQ ID NO:6. Therefore, while the claims are not so limited, it is not apparent that the human IL-21 polynucleotide would have a similar effect on human NK cells.

Furthermore, the claims are not solely directed to a polynucleotide encoding the polypeptides of SEQ ID NO: 6 or SEQ ID NO: 8, but rather to a larger plurality of structural and/or functional variants thereof, or mere fragments of these polypeptides consisting of as few as 5 amino acids[2]. Just as one cannot predict whether contacting any of a plurality of natural killer cells isolated from various different animals with a nucleic acid encoding the human polypeptide of SEQ ID NO: 6 will be effective to induce the apoptosis in those cells, one cannot predict whether variants or fragments of the polypeptides of SEQ ID NO: 6 or SEQ ID NO: 8 will have such an effect on those same cells. Even so, many of fragments of the mouse polypeptide of SEQ ID NO: 8, and especially those which consist of as few as 5 amino acids, are reasonably expected to *lack* the activity of the full-length polypeptide; notably there is little or no guidance in the specification that would enable the skilled artisan to select variants and fragments of the polypeptide of SEQ ID NO: 8 that have or retain the ability of the polypeptide of SEQ ID NO: 8 to induce the apoptosis in mouse natural killer cells.

[2] See, e.g., the specification at paragraph [0026] of the published application.

Accordingly, contrary to Applicant's arguments, for these reasons and as explained more fully in the Office action mailed January 18, 2007, the specification as filed does not enable the claimed methods of inducing apoptosis of a natural killer (NK) cell. Thus, as the specification has failed to reasonably enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation, this rejection is maintained.

Response to the Amendment

13. The amendment filed August 8, 2007, is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: SEQ ID NOs: 6, 7, 8, and 9 of the substitute Sequence Listing.

At page 11 of the amendment filed August 8, 2007, Applicant has remarked that the substitute Sequence Listing is "the same as the one submitted on September 24, 2004, except that the one submitted herewith includes the amino acid sequence WSXWS, and the sequences of GenBank[™] Accession Nos. AAG29348, AF254069, AAG29349, and AF254070, which sequences were incorporated by reference".

Presumably it is Applicant's position that the sequences set forth in GenBank™ accession numbers AAG29348, AF254069, AAG29349, and AF254070 are properly incorporated by reference in this application to those sequences at paragraph [0021] of the specification, as filed.

However, Applicant is reminded that M.P.E.P. § 608.01(p) does not provide for the incorporation by reference of essential material by reference to non-patent publications, such as the information contained in sequence databases. "Essential material" is defined as "that which is necessary to (1) describe the claimed invention, (2) provide an enabling disclosure of the claimed invention, or (3) describe the best mode (35 U.S.C. 112)". The amino sequences to which the claims are directed is essential information, which is necessary to both describe and enable the claimed invention.

Therefore, if Applicant intends that information contained in GenBank™ under any of accession numbers AAG29348, AF254069, AAG29349, and AF254070 be incorporated, Applicant is required to amend the specification to include the material incorporated by reference; **and** the amendment must be accompanied by an affidavit or declaration executed by Applicant, or a practitioner representing Applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

If this issue is not otherwise appropriately remedied, Applicant is required to cancel the new matter in the reply to this Office Action.

New Grounds of Objection

Specification

14. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required:

Claims 59, 66, and 67 are directed to a process comprising contacting natural killer cells with a polynucleotide encoding SEQ ID NO: 6 or 8, a variant of SEQ ID NO: 6 or 8, wherein the variant has an amino acid sequence that is greater than 95% identical to the amino acid sequence of SEQ ID NO: 6 or 8, or a fragment of about 5 to about 30 amino acids of SEQ ID NO: 6 or 8, wherein the fragment retains the biological activity of SEQ ID NO: 6 or 8.

The specification, as filed, however does not provide antecedent basis for such language.

In accordance with 37 C.F.R. § 1.78, the claim or claims must conform to the invention as set forth in the remainder of the specification and the terms and phrases used in the claims must find clear support or antecedent basis in the description so that the meaning of the terms in the claims may be ascertainable by reference to the description.

This is necessary in order to insure certainty in construing the claims in the light of the specification, *Ex parte Kotler,* 1901 C.D. 62, 95 O.G. 2684 (Comm'r Pat. 1901). See 37 C.F.R. § 1.75, M.P.E.P. §§ 608.01(i) and 1302.01.

M.P.E.P. § 608.01(o) states:

> While an applicant is not limited to the nomenclature used in the application as filed, he or she should make appropriate amendment of the specification whenever this nomenclature is departed from by amendment of the claims so as to have clear support or antecedent basis in the specification for the new terms appearing in the claims. This is necessary in order to insure certainty in construing the claims in the light of the specification, *Ex parte Kotler,* 1901 C.D. 62, 95 O.G. 2684 (Comm'r Pat. 1901). See 37 CFR 1.75, MPEP § 608.01(i) and § 1302.01.

M.P.E.P. § 608.01(o) further states that if the examiner determines that the claims presented late in prosecution do not comply with 37 CFR 1.75(d)(1), applicant will be required to make appropriate amendment to the description to provide clear support or antecedent basis for the terms appearing in the claims provided no new matter is introduced.

It is submitted that it would not be clear from a reading of the descriptive portion of this application, alone, where there is support for the language of the claims because apart from the listing of the amino acid sequences of SEQ ID NOs: 6 and 8 in the present Sequence Listing, there is no other reference to this sequence in the disclosure.

Accordingly, because the disclosure, as filed, does not provide proper antecedent basis for the language of the claims, Applicant is required to correct this deficiency by appropriately amending the specification without introducing new matter and in accordance with M.P.E.P. § 608.01(o).

Claim Objections

15. Claim 67 is objected to, as it appears to omit the word "of" between the words "method inducing" in the first line of the claim.

Appropriate correction is required.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

16. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

17. Claim 67 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 67 is indefinite in the recitation of "wherein the fragment retains the *biological activity* of SEQ ID NO:6 or 8". This recitation renders the claim indefinite because polypeptides comprising the amino acid sequence of SEQ ID NO:6 or 8 are expected to have multiple biological activities and it is unclear to which biological activity the claim is directed. Which of the expected plurality of biological activities of the polypeptides SEQ ID NO:6 or 8 must be retained by the fragment? The claims cannot be construed unambiguously without knowing the answer to this question. Thus, the claim fails to delineate the subject matter that Applicant regards as the invention with the requisite degree of clarity and particularity to permit the skilled artisan to know or determine infringing and non-infringing subject matter and thereby satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph.

Accordingly, this claim is indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

18. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

19. Claims 66 and 67 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description" Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

In the instant case, claims 66 and 67 are drawn to genera of "polynucleotides encoding, (i) a variant of SEQ ID NO: 6 or 8, wherein the variant has an amino acid sequence that is greater than 95% identical to the amino acid sequence of SEQ ID NO: 6 or 8, or (ii) a fragment of about 5 to about 30 amino acids of SEQ ID NO: 6 or 8, wherein the fragment retains the biological activity of SEQ ID NO: 6 or 8". The claims do not require that the polypeptide possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature.

Thus, the claims are broadly, but reasonably interpreted as encompassing an extremely large genus of structurally and functionally diverse polynucleotides that encode polypeptides that are defined only by sequence identity to SEQ ID NO: 6 or 8 that can induce apoptosis of natural killer cells, that do not necessarily retain any structural or functional similarity to the particularly described murine interleukin 21 polynucleotide that encodes SEQ ID NO:8 or human interleukin 21 polynucleotide that encodes SEQ ID NO:6.

Therefore, the written description of the present application does not reasonably convey that Applicant was in possession of the claimed because the specification does not describe the structure of a sufficient number of species of the genera of "polynucleotides encoding, (i) a variant of SEQ ID NO: 6 or 8, wherein the variant has an amino acid sequence that is greater than 95% identical to the amino acid sequence of SEQ ID NO: 6 or 8, or (ii) a fragment of about 5 to about 30 amino acids of SEQ ID NO: 6 or 8, wherein the fragment retains the biological activity of SEQ ID NO: 6 or 8" that are encompassed by the disclosure of the specification to reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Notably, at page 13, last paragraph of the response filed August 8, 2007, Applicants submits that one of skill in the art could immediately envision the newly presented genera of claims 66 and 67, given their structural and functional features.

In response, the specification does not describe with any particularity the identifying structural and/or functional features of the polynucleotide variants or fragments to which the claims are directed, nor does it describe with particularity the polypeptides that are encoded by these polynucleotides. In this case, specific guidance identifying structural features of the polypeptides that are encoded by these polynucleotides which correlates with their ability to induce apoptosis is needed to provide adequate support for these genera, because it is well-established in the art that there is a high degree of unpredictability in determining the three-dimensional structure of a given protein *a priori* and the function of a given protein is also highly unpredictable and variable and cannot necessarily be linked to a given structure.

For example, it is established in the art that there is a high degree of unpredictability in determining the structure of a given protein because a protein's structure is dependent on its given amino acid sequence and cannot be determined *a priori* and the function of a given protein is also highly unpredictable and variable and cannot necessarily be linked to a given structure. As evidenced by Jones (Pharmacogenomics Journal, 1:126-134, 2001), protein structure "prediction models are still not capable of producing accurate models in the vast majority of cases" (page 133,

3rd paragraph). Furthermore, Tosatto et al state, "the link between structure and function is still an open question and a matter of debate" (Current Pharmaceutical Design, 12:2067-2086, 2006, page 2075, 1st new paragraph). Therefore, the structure and function of the polypeptides that are 95% identical to the amino acid sequence of SEQ ID NO: 6 or 8 or fragments of about 5 to about 30 amino acids of SEQ ID NO: 6 or 8 is highly unpredictable and as a consequence the functions of nucleic acids that encode them are also highly unpredictable given just the disclosure of the polynucleotide that encodes SEQ ID NO:8 which induces apoptosis of murine NK cells when comprised in a plasmid and injected into mice. Therefore, it is submitted that one of skill in the art would not be able to immediately envision or recognize which polynucleotides encoding, (i) a variant of SEQ ID NO: 6 or 8, wherein the variant has an amino acid sequence that is greater than 95% identical to the amino acid sequence of SEQ ID NO: 6 or 8, or (ii) a fragment of about 5 to about 30 amino acids of SEQ ID NO: 6 or 8, wherein the fragment retains the biological activity of SEQ ID NO: 6 or 8 would actually induce apoptosis in NK cells.

In support of this conclusion, Skolnick et al. (*Trends in Biotechnology* 2000; 18: 34-39), for example, discloses that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (see, e.g., the abstract; and page 34, *Sequence-based approaches to function prediction*). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see, in particular, the abstract and Box 2).

In addition, Bowie et al. (*Science* 257: 1306-1310, 1990) teaches that an amino acid sequence encodes a message that determines the shape and function of a protein; and, that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome. Bowie et al. teaches that the determination of protein structure from sequence data and, in turn, utilizing structural determinations to ascertain functional aspects of the protein is extremely complex (page 1306, column 1). Even if the skilled artisan were able to

submit a complete list of all the possible polynucleotides that encode these protein variants and fragments, which fall within the scope of the claims, the skilled artisan could not recognize which of these polynucleotides would encode protein variants or fragments that can induce apoptosis in NK cells, and which would not.

Thus, one skilled in the art would not accept the assertion, which is based only upon an observed similarity in amino acid sequence, that proteins that are 95% identical to the amino acid sequence of SEQ ID NO: 6 or 8 or protein fragments of about 5 to about 30 amino acids of SEQ ID NO: 6 or 8 are functionally equivalent to the polypeptide of SEQ ID NO: 6 or 8, respectively, or even have a structure that is substantially equivalent to that of the polypeptide of SEQ ID NO: 6 or 8, respectively.

In addition, the skilled artisan cannot reliably and accurately predict or recognize the functional and structural consequences of amino acid differences in two proteins; but the more structurally disparate a given protein, the less likely the protein will share the function of structurally related proteins having known functions. Burgess et al. (*Journal of Cell Biology* 1990; 111: 2129-2138) exemplifies the sensitivity of proteins to alterations of even a single amino acid in a sequence. Burgess et al. teaches that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. As another example of this sensitivity to amino acid sequence variations, Lazar et al. (*Molecular and Cellular Biology*, 1988, 8: 1247-1252) teaches that a replacement of aspartic acid at position 47 with alanine or asparagine in transforming growth factor alpha had no effect but that a replacement with serine or glutamic acid sharply reduced its biological activity. Thus, Lazar et al. teaches that even a single *conservative* amino acid substitution may adversely affect the function of a protein.

Even more recently, Guo et al. (*Proc. Natl. Acad. Sci. USA.* 2004 Jun 22; 101 (25): 9205-9210) have calculated the probability that a random amino acid substitution, such as that which might occur naturally during aging or as a consequence of evolution or disease, will cause inactivation of a protein; see entire document (e.g., the abstract). Guo et al. reports this probability was found to be 34% ± 6% (abstract); that is, 34% of

random mutations in the sequence of a protein are predicted to cause the inactivation of the protein. Guo et al. observed that various residues are differentially sensitive to substitutions, but the tolerance of the entire protein to random change can be defined by the probability that any given random amino acid substitution will inactivate the protein (i.e., the so-called "*x* factor") (page 9209, column 2). Not surprisingly, evolutionarily conserved residues showed low substitutability indices (abstract).

Thus, Lazar et al, for example, shows that even a single amino acid change can cause substantial changes in the activity of a protein, so it is evident that the skilled artisan cannot predict the functional consequences of amino acid substitutions and must determine those consequences empirically; and since Guo et al. shows that amino acid substitutions are remarkably likely to cause inactivation of the protein, it is even more apparent that the functional consequences of the amino acid differences must be ascertained before any given variant of a protein can be used in the same manner in which the protein having a known function is used and therefore polynucleotides encoding these variants or fragments of a protein similarly could not be used in the same manner in which the polynucleotide encoding a protein having a known function is used.

Accordingly, the genera of "polynucleotides encoding, (i) a variant of SEQ ID NO: 6 or 8, wherein the variant has an amino acid sequence that is greater than 95% identical to the amino acid sequence of SEQ ID NO: 6 or 8, or (ii) a fragment of about 5 to about 30 amino acids of SEQ ID NO: 6 or 8, wherein the fragment retains the biological activity of SEQ ID NO: 6 or 8"" includes members, having substantially and significantly variant structures and/or functions. The specification fails to adequately describe this genus, as a whole, because the skilled artisan could not immediately envision, recognize or distinguish at least most of its members, as the specification fails to describe its members as sharing any particularly identifying (i.e., substantial) structural feature, which correlates with any one particularly identifying functional feature that is also shared by many, if not all, of those polypeptides.

Finally, while the fragments of SEQ ID NO: 6 or 8 are required to retain the biological activity of SEQ ID NO:6 or 8, it is submitted that one of skill in the art could

not immediately envision which fragments of SEQ ID NO:6 or 8 retain a biological activity of a polypeptide of SEQ ID NO:6 or 8 as the specification does not describe with any particularity any fragments or domains of SEQ ID NO:6 or 8 that retain any biological activity of a polypeptide of SEQ ID NO:6 or 8.

Furthermore, it is aptly noted that the Federal Circuit has decided that a generic statement that defines a genus of substances by *only* their functional activity, i.e., having a biological activity of a polypeptide of SEQ ID NO:6 or 8 or being capable of inducing apoptosis of natural killer cells, does not provide an adequate written description of the genus. See *The Reagents of the University of California v. Eli Lilly*, 43 USPQ2d 1398 (CAFC 1997). The Court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a precise definition of a representative number of members of the genus, such as by reciting the structure, formula, chemical name, or physical properties of those members, rather than by merely reciting a wish for, or even a plan for obtaining a genus of molecules having a particular functional property. The recitation of a functional property alone, which must be shared by the members of the genus, is merely descriptive of what the members of genus must be capable of doing, not of the substance and structure of the members.

Although *Lilly* related to claims drawn to genetic material, the statute applies to all types of inventions. "Regardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to the subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods". *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1984 (CAFC 2004).

"[G]eneralized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004). Here, there is no language that adequately describes the genera of "polynucleotides" to which the claims are directed.

Again, the genera of "polynucleotides encoding, (i) a variant of SEQ ID NO: 6 or 8, wherein the variant has an amino acid sequence that is greater than 95% identical to the amino acid sequence of SEQ ID NO: 6 or 8, or (ii) a fragment of about 5 to about 30 amino acids of SEQ ID NO: 6 or 8, wherein the fragment retains the biological activity of SEQ ID NO: 6 or 8" as encompassed by the claims do not share a disclosed common structural feature that relates to their ability of being capable of inducing apoptosis of natural killer cells.

Although the skilled artisan could potentially screen for other polynucleotides encompassed by the claims that could be used induce apoptosis of natural killer cells, it is duly noted that the written description provision of 35 U.S.C § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

Given the lack of particularity with which the "polynucleotides", to which the claims are directed, are described in the specification, it is submitted that the skilled artisan could not immediately envision, recognize or distinguish at least most of the members of the genera of "polynucleotides encoding, (i) a variant of SEQ ID NO: 6 or 8, wherein the variant has an amino acid sequence that is greater than 95% identical to the amino acid sequence of SEQ ID NO: 6 or 8, or (ii) a fragment of about 5 to about 30 amino acids of SEQ ID NO: 6 or 8, wherein the fragment retains the biological activity of SEQ ID NO: 6 or 8" to which the claims are directed; and therefore the specification

would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

20. Claims 59, 66, and 67 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "new matter" rejection.

Claims 59, 66, and 67 are directed to a process comprising contacting natural killer cells with a polynucleotide encoding SEQ ID NO: 6 or 8, a variant of SEQ ID NO: 6 or 8, wherein the variant has an amino acid sequence that is greater than 95% identical to the amino acid sequence of SEQ ID NO: 6 or 8, or a fragment of about 5 to about 30 amino acids of SEQ ID NO: 6 or 8, wherein the fragment retains the biological activity of SEQ ID NO: 6 or 8.

At page 11 of the amendment filed August 8, 2007, Applicant has remarked that the substitute Sequence Listing is "the same as the one submitted on September 24, 2004, except that the one submitted herewith includes the amino acid sequence WSXWS, and the sequences of GenBank[™] Accession Nos. AAG29348, AF254069, AAG29349, and AF254070, which sequences were incorporated by reference".

Presumably it is Applicant's position that the sequences set forth in GenBank™ accession numbers AAG29348, AF254069, AAG29349, and AF254070 are properly incorporated by reference in this application to those sequences at paragraph [0021] of the specification, as filed.

However, as explained above, M.P.E.P. § 608.01(p) does not provide for the incorporation by reference of essential material by reference to non-patent publications, such as the information contained in sequence databases. "Essential material" is defined as "that which is necessary to (1) describe the claimed invention, (2) provide an enabling disclosure of the claimed invention, or (3) describe the best mode (35 U.S.C.

112)". The amino sequences to which the claims are directed is essential information, which is necessary to both describe and enable the claimed invention.

Because M.P.E.P. § 608.01(p) does not provide for the incorporation by reference of essential material by reference to non-patent publications, if Applicant intends that information, such as the amino acid sequences of SEQ ID NO: 6 and 8, which is contained in this non-patent publication be incorporated, Applicant is required to amend the specification to include the material that is incorporated by reference.

The amendment must be accompanied by an affidavit or declaration executed by Applicant, or a practitioner representing Applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

A provision of such an affidavit or declaration assuring that the amendatory material consists of the same material incorporated by reference in the referencing application would be remedial.

Conclusion

21. No claim is allowed.

22. Applicant's amendment necessitated the new ground(s) of rejection and objection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brad Duffy whose telephone number is (571) 272-9935. The examiner can normally be reached on Monday through Friday 7:00 AM to 4:30 PM, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully,
Brad Duffy
571-272-9935

/Stephen L. Rawlings/
Stephen L. Rawlings, Ph.D.
Primary Examiner, Art Unit 1643

bd
October 14, 2007